Institute Report No. 347

Acute Dermal Toxicity of Trimethylolethane Trinitrate (TMETN) in Rabbits

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MAMMALIAN TOXICOLOGY BRANCH
DIVISION OF TOXICOLOGY

July 1989

Toxicology Series: 119

LETTERMAN ARMY INSTITUTE OF RESEARCH
PRESIDIO OF SAN FRANCISCO, CALIFORNIA 94129

Acute Dermal Toxicity of Trimethylolethane Trinitrate (TMETN) in Rabbits (Toxicology Series 119)--Morgan and Korte

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Richard A. Kishimoto — 20 July 1983

Richard A. Kishimoto (date)
COL, MSC
Acting Commander

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The acute dermal toxicity of trimethylolethane trinitrate, TMETN, was evaluated in five male and five female New Zealand White rabbits. Neat TMETN (2 g/kg) was applied topically to the clipped dorsal skin surface under a semi-occlusive wrap for 24 hours. No evidence was obtained of percutaneous absorption of quantities sufficient to produce systemic toxicity or death. Seven of the rabbits exhibited very slight to slight erythema after wrap removal and all but one had cleared by 48 hours. In this animal erythema persisted for 5 days after wrap removal. These data indicate that TMETN does not produce systemic toxicity when administered by 24-hour topical application at a limit dose of 2 g/kg..

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ABSTRACT

The acute dermal toxicity of trimethylolethane trinitrate, TMETN, was evaluated in five male and five female New Zealand White rabbits. Neat TMETN (2 g/kg) was applied topically to the clipped dorsal skin surface under a semi-occlusive wrap for 24 hours. No evidence was obtained of percutaneous absorption of quantities sufficient to produce systemic toxicity or death. Seven of the rabbits exhibited very slight to slight erythema after wrap removal and all but one had cleared by 48 hours. In this animal erythema persisted for 5 days after wrap removal. These data indicate that TMETN does not produce systemic toxicity when administered by 24-hour topical application at a limit dose of 2 g/kg.

KEY WORDS: Acute Dermal Toxicity, Trimethylolethane Trinitrate, TMETN, Rabbit, Propellant, Mammalian Toxicology

PREFACE

TYPE REPORT: Acute Dermal Toxicity GLP Report

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Letterman Army Institute of Research
Presidio of San Francisco, CA 94129-6800

SPONSOR:

US Army Medical Research and Development Command
US Army Biomedical Research and Development Laboratory
Fort Detrick, MD 21701-5010
Project Officer: Gunda Reddy, PhD

PROJECT/WORK UNIT/APC: 3E162720A835/180/TLB0

GLP STUDY NUMBER: 84038

STUDY DIRECTOR: Don W. Korte, Jr., PhD, LTC, MSC
Diplomate, American Board of Toxicology

PRINCIPAL INVESTIGATOR: Earl W. Morgan, DVM, MAJ, VC
Diplomate, American College of
Veterinary Preventive Medicine,
American Board of Toxicology

PATHOLOGIST: Lance O. Lollini, DVM, LTC, VC
Diplomate, American College of Veterinary
Pathologists

REPORT AND DATA MANAGEMENT:

A copy of the final report, study protocols, raw data, retired SOPs, and an aliquot of the test compound will be retained in the LAIR Archives.

TEST SUBSTANCE: Trimethylolethane Trinitrate (TMETN)

INCLUSIVE STUDY DATES: 11 October 1984 - 13 November 1984

OBJECTIVE:

The objective of this study was to evaluate the acute dermal toxicity of TMETN in male and female New Zealand White rabbits.

ACKNOWLEDGMENTS

LTC Larry D. Brown, DVM, SP4 James J. Fischer, and SP4 Scott L. Schwebe assisted in conducting this research; SP4 Theresa L. Polk, Diane Arevalo, Charlotte L. Speckman, and Richard A. Spieler provided care for the animals; SGT Paul B. Simboli, BS, assisted in the chemical analysis; and Colleen S. Kamiyama and Dorothy Davis provided secretarial assistance.

SIGNATURES OF PRINCIPAL SCIENTISTS INVOLVED IN THE STUDY

We, the undersigned, declare that GLP Study 84038 was performed under our supervision, according to the procedures described herein, and that this report is an accurate record of the results obtained.

Don W. Korte 10 July 89

DON W. KORTE, JR., PhD/ DATE
LTC, MS
Study Director

Earl W. Morgan 2 Jul 89

EARL W. MORGAN, DVM/ DATE
MAJ, VC
Principal Investigator

Conrad Wheeler 10 July 89

CONRAD WHEELER, PhD/ DATE
DAC
Analytical Chemist

DEPARTMENT OF THE ARMY

LETTERMAN ARMY INSTITUTE OF RESEARCH
PRESIDIO OF SAN FRANCISCO, CALIFORNIA 94129-0800

REPLY TO
ATTENTION OF:

SGRD-ULZ-QA

10 July 1989

MEMORANDUM FOR RECORD

SUBJECT: GLP Compliance for GLP Study 84038

1. This is to certify that the protocol for LAIR GLP Study 84038 was reviewed on 15 October 1984.

2. The institute report entitled "Acute Dermal Toxicity of Trimethylolethane Trinitrate (TMETN) in Rabbits," Toxicology Series 119, was audited on 5 July 1989.

Carolyn M. Lewis

CAROLYN M. LEWIS, MS
Diplomate, American Board of Toxicology
Quality Assurance Auditor

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Acute Dermal Toxicity of Trimethylolethane Trinitrate (TMETN) in Rabbits—
Morgan and Korte

INTRODUCTION

The Department of Defense is considering the use of diethyleneglycol dinitrate (DEGDN), triethyleneglycol dinitrate (TEGDN), or trimethylolethane trinitrate (TMETN) as a replacement for nitroglycerin in new propellant formulations. However, considerable gaps in the toxicology data of the compounds were identified during a review of their health effects (1) conducted for the US Army Biomedical Research and Development Laboratory (USABRDL). Consequently, USABRDL has tasked the Division of Toxicology, Letterman Army Institute of Research (LAIR), to conduct an initial health effects evaluation of the proposed replacement nitrate esters. This initial evaluation of DEGDN, TMETN, TEGDN, and two DEGDN-based propellants, JA-2 and DIGL-RP, includes the Ames mutagenicity assay, acute oral toxicity tests in rats and mice, acute dermal toxicity studies in rabbits, dermal and ocular irritation studies in rabbits, and dermal sensitization studies in guinea pigs.

Objective of Study

The objective of this study was to determine the acute dermal toxicity of trimethylolethane trinitrate (TMETN) in male and female New Zealand White rabbits.

MATERIALS

Test Substance

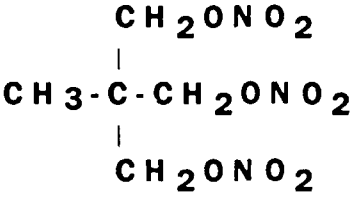
Chemical Name: Trimethylolethane trinitrate (TMETN)

Chemical Abstracts Service Registry No.: 3032-55-1

LAIR Code Number: TA35

Physical State: Oily brown liquid

Chemical Structure:



Molecular Formula: $C_5H_9N_3O_9$

Source: Naval Ordnance Station, Indian Head, MD

Other test substance information is presented in Appendix A.

Vehicle

No vehicle was required as TMETN is a liquid at room temperature.

Animal Data

Five male and five female young New Zealand White rabbits (Elkhorn Rabbitry, Watsonville, CA) from a shipment that arrived at LAIR on 11 October 1984 were assigned to the study. One rabbit (84F604) in the shipment was submitted for necropsy quality control on 12 October 1984. The 10 rabbits were identified individually by ear tattoos. The animal weights ranged from 2.0 to 2.4 kg on receipt and from 2.5 to 3.0 kg at dosing. Additional animal data appear in Appendix B.

Husbandry

The rabbits were housed individually in stainless steel wire mesh cages in racks equipped with automatic flushing dumptanks. No bedding was used in any of the cages. Water was provided *ad libitum* by continuous drip from a central line. The diet consisted of approximately 150 g per day of Purina Certified Rabbit Chow® No. 5322 (Ralston Purina Company, St. Louis, MO). The animal room temperature was maintained at 15.0-18.9°C and the relative humidity was maintained at 56% to 78%, except for minor fluctuations due to room cleaning. The photoperiod was 12 hours of light per day.

METHODS

This study was performed in accordance with LAIR Standard Operating Procedure OP-STX-30, "Acute Dermal Toxicity Study" (2) and Environmental Protection Agency guidelines (3).

Acclimation/Group Assignment

Study rabbits were quarantined by the Division of Animal Care and Services, LAIR, for two weeks before being certified healthy by a staff veterinarian. During quarantine the rabbits were given one application of Canex®/mineral oil (Pitman-Moore, Inc., Washington Crossing, NJ) for ear mite protection. After being certified healthy, the rabbits were transferred to the Toxicology Suite for the remainder of the study.

Randomization for group assignment was unnecessary as there was only one dose level for each sex.

Dose Levels

A "limit test" was conducted in which 5 male and 5 female rabbits were assigned to a test group receiving 2.0 g/kg of TMETN applied topically to the dorsum (skin over back). According to body weight, 3.4 to 4.1 ml of neat TMETN was applied to each rabbit.

Compound Preparation

TMETN was received as a 10% solution in ethanol. The ethanol was removed by rotoevaporation leaving neat TMETN. Since neat TMETN is a liquid, no further preparation was required.

Chemical Analysis of TMETN

Periodic analysis of the ethanol solutions and neat TMETN by HPLC analysis has shown no evidence of decomposition for up to 9 weeks. Since the neat TMETN contained no impurities as determined in a nuclear magnetic resonance analysis and 98% of the TMETN chromatographed as a single peak by HPLC, it was considered to be at least 98% pure.

Test Procedures

The application sites on the dorsal and lateral sections of the animals (surface area approximately 300 cm^2) were close-clipped with electric clippers (Oster® Model A5, Size 40 blade, Sunbeam Corp, Milwaukee, WI) 24 hours before appling the test compound. The animals were weighed, and the volume of compound required to provide the 2.0 g/kg limit dose was measured. This quantity of the test compound was evenly distributed over the surface of an 7 x 7 in. piece of gauze dressing (Curity Cover Sponges. Kendall Co. Hospital Products, Boston, MA) which was then taped to the animal's back with hypoallergenic tape (Durapore® Surgical Tape, 3M Corp, St. Paul, MN). The trunk of the animal was then wrapped with Vetrap® bandaging tape (Animal Care Products, 3M Corp, St. Paul, MN) to hold the compound in place and prevent the animal from ingesting the compound. The Vetrap® was anchored in place cranially and caudally by strips of Conform® elastic tape (Kendall Co. Hospital Products, Boston, MA). The patch and wrappings were left in place for 24 hours. No restraint of the animals was used except during the wrapping procedure. When the wrappings and patch were removed, the exposed area was gently wiped with a piece of saline-moistened gauze to remove any remaining test compound.

Observations

Observations for mortality and signs of acute toxicity were performed daily according to the following procedure: (1) animals were observed undisturbed in their cages, (2) animals were removed from their cages and given a physical examination, and (3) animals were observed after being returned to their cages. On the day of dosing, the animals were checked intermittently throughout the day. Observations were recorded daily for the remainder of the two-week test period. A second "walk through" observation was performed each day, with only significant observations recorded. The exposed area was examined daily after patch removal, and all lesions were noted and graded as described below. Animals were weighed weekly during the study test period.

During evaluation of the exposure site, area and intensity of each dermal reaction were graded. Grading was performed according to a scale which included five categories to describe area and severity. Area categories were 0 - 5%, > 5 - 10%, > 10 - 25%, > 25 - 50% and > 50%; severity was defined as very slight, slight, moderate, well-defined, and severe.

Necropsy

All study animals were submitted for necropsy. Those that survived the 14-day study period were necropsied immediately after being given an overdose of sodium pentobarbital and sacrificed by exsanguination from severed axillary vessels. Skin was taken from the exposed area and examined microscopically.

Duration of Study

The study period was 14 days and was preceded by a 19-day quarantine. Historical study events are listed in Appendix C.

Changes/Deviations from Protocol

The hygrothermograph used in the animal room was not wound properly so that the timing mechanism lost approximately a day each week. There was a steam outage in the building on 30 October with a resulting fluctuation in the temperature (up to 78°C) and humidity (down to 20%) readings during the day. None of these changes appeared to have any effect on the study.

Raw Data and Final Report Storage

A copy of the final report, study protocols, raw data, retired SOPs, and an aliquot of the test compound will be retained in the LAIR Archives.

RESULTS

Twenty-four hour dermal exposure to TMETN at a limit dose of 2.0 g/kg produced no mortality in the 10 rabbits evaluated in the study. During the course of the study, observations were split into two major categories: systemic (general health of the animal) and dermal.

Systemic: Rabbit 84F608 had a marked purulent exudate in the right ear canal and exhibited slight to moderate torticollis to the right from Day 8 through Day 14 of the study. Three rabbits (84F610, 84F614, 84F617) had diarrhea and/or fecal material matted in the perianal areas. The diarrhea was first observed approximately 2 hours after dosing in the first 2 rabbits and had resolved by 24 and 48 hours after dosing, respectively. In rabbit 84F617, the fecal material matted in the fur in the perianal area was first recorded on Day 1 and persisted through the end of the study with the exception of Days 11 and 12 after dosing. Rabbit 84F610 also had slight conjunctival redness on the day of dosing. One male (84F617) pulled hair from his abdomen and flank from Day 3 through termination of the study. The hair pulling did not involve the dosed area. None of the clinical systemic signs were interpreted as signs of toxicity attributable to TMETN. The rabbits gained weight, as expected for young animals, during quarantine and after administration of TMETN (Appendix D).

Dermal: Skin irritation signs are presented in Appendix E. Erythema, observed in 7 of 10 rabbits, was the only dermal response to TMETN. By 24 hours the erythema had disappeared in all but 2 animals. Rabbit 84F608 was clear of erythema by 48 hours after dosing. Slight erythema persisted in rabbit 84F615 through 96 hours.

There were no gross or microscopic findings in these rabbits at necropsy, following the 2-week observation period, that could be attributed to dermal exposure to TMETN at the 2 ml/kg dose level. Otitis media was confirmed in rabbit 84F608 and malocclusion of the teeth was observed in rabbit 84F617. A copy of the complete Pathology Report appears in Appendix F.

DISCUSSION

Acute dermal toxicity testing is designed to evaluate both systemic toxicity due to percutaneous absorption of the test material and local toxicity from its contact with the skin. From these observations it can be determined whether absorption of the test material across the skin is sufficient to produce systemic effects or lethality. In the present study, trimethylolethane trinitrate produced slight local dermal reactions with no evidence of systemic effects.

All of the animals exposed to a limit dose of 2.0 g/kg TMETN survived to the end of the test. None of these test animals exhibited any clinical signs suggestive of a systemic action by TMETN. This lack of dermal systemic toxicity is in marked contrast with the results of the acute oral toxicity studies. In the acute oral toxicity studies the median lethal dose was determined to be 655.4 (female) and 828.6 (male) mg/kg for CD-1 mice and 1027.4 (female) and 1587.3 (male) mg/kg for Sprague-Dawley rats (4). Therefore, it is concluded that dermal exposure to TMETN, at 2.0 g/kg, either does not result in sufficient percutaneous absorption to produce systemic toxicity or is not a systemic toxin at doses tested in the rabbit. The dermal median lethal dose of TMETN, as indicated by this study, is above the limit value of 2.0 g/kg.

Local dermal toxicity was observed at the site of exposure. As summarized in Appendix E, very slight to slight erythema was present in 7 of 10 animals after the removal of test compound wrappings.

CONCLUSION

A limit dose of 2.0 g/kg trimethylolethane trinitrate was not lethal to rabbits nor did it produce significant systemic effects following dermal exposure for 24 hours.

REFERENCES

1. Holleman JW, Ross RH, Carroll JW. Problem definition study on the health effects of diethyleneglycol dinitrate, triethyleneglycol dinitrate, and trimethylolethane trinitrate and their respective combustion products. Frederick, MD: US Army Medical Bioengineering Research and Development Laboratory, 1983, DTIC No. ADA 127846.

2. Acute dermal toxicity study. LAIR Standard Operating Procedure OP-STX-30, Presidio of San Francisco, CA: Letterman Army Institute of Research, 18 May 1984.

3. Environmental Protection Agency. Office of Pesticides and Toxic Substances, Office of Toxic Substances (TS-792). Acute exposure, dermal toxicity. In: Health effects test guidelines. Washington, DC: Environmental Protection Agency, August 1982; EPA 560/6-82-001.

4. Brown LD, Hiatt GFS, Morgan EW, Wheeler CR, Lewis CM, Johnson YC, Ryabik JRG, Okerberg CV, Makovec GT, Lollini LO, Mellick PW, Korte DW, Jr. Acute toxicity of TEGDN and TMETN liquid propellants. Laurel, MD: Chemical Propulsion Information Agency, 1985; CPIA Publication 436, p. 313-320.

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Appendix A: CHEMICAL DATA

Chemical Name: 1,3-Propanediol, 2-methyl-2[(nitrooxy)methyl]-dinitrate (ester)

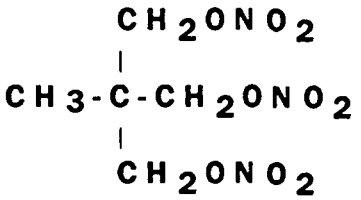
Other Names: 1,3-Propanediol-2-(hydroxymethyl)-2-methyl-, trinitrate;
1,1,1-Trimethylolethane trinitrate(TMETN),
Metriol trinitrate (MTN); Nitropentaglycerin

Lot Number: 53-84A

Chemical Abstracts Service Registry No.: 3032-55-1

LAIR Code No.: TA35

Structural Formula:



Molecular Formula: $C_5H_9N_3O_9$

Molecular Weight: 255.15

Physical State: Light brown oil

Melting Point: -3° [1,2]

Compound Density: 1.47 g/cm [1,2]

Source: Naval Ordnance Station, Indian Head, MD, 20640

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[1] Holleman JW, Ross RH, Carroll JW. Problem definition study on the health effects of diethyleneglycol dinitrate, triethyleneglycol dinitrate, and trimethylolethane trinitrate and their respective combustion products. Frederick, MD: US Army Medical Bioengineering Research and Development Laboratory, 1983, DTIC No. ADA 127846, p. 17.

[2] Lindner V. Properties of explosive aliphatic nitrate esters. Table 5. In: Grayson M., exec. ed. Kirk-Othmer Encyclopedia of Chemical Technology. Volume 9. 3rd ed. New York: John Wiley and Sons, Inc., 1980:573.

Appendix A (cont.): CHEMICAL DATA

Analytical Data: Ultraviolet (UV) spectra were obtained using a Hitachi 110-A Spectrophotometer (Hitachi Instruments, Inc., Mountain View, CA), infrared spectra (IR) were obtained with a Perkin-Elmer Model 457 Infra-red Spectrophotometer (Perkin-Elmer, Norwalk, CT) and nuclear magnetic resonance (NMR) spectra were recorded on a Varian FT-80 NMR (Varian, Palo Alto, CA) using tetramethylsilane as an internal standard. Chromatographic analysis was performed using a 1090B HPLC with diode array detector (Hewlett-Packard, Santa Clara, CA) and a Brownlee RP-18 Spheri-5 Column, 4.6 x 250 mm (Brownlee Labs, Inc., Santa Clara, CA). The following conditions were employed for the HPLC assay: solvent system, 70% methanol, 30% water; flow rate, 0.9 ml/min; detector wavelength, 215 nm; oven temperature, 50°C.

UV Spectrum: For UV analysis TMETN was dissolved in acetonitrile. UV absorbance begins at approximately 240 nm and increases with decreasing wavelength.[3] No absorption peak was observed. IR (KBr windows): 2900, 1645 (asymmetric stretch of NO group, 1470, 1375, 1280 (symmetric stretch of NO_2 group), 990, 860, and 755 cm.[4] ^1H NMR (CDCl, 80 MHz): d 1.22 (S, 3H, $C\underline{H}_3$), 4.44 (S, 6H, -$C\underline{H}_2$-).[5] TMETN subjected to HPLC analysis eluted as two peaks with retention times of 5.5-5.6 and 12.5 min.[6] Based on integration of peak areas the first peak represented 98% of the sample. The second peak was not identified. No decomposition of TMETN was detected by HPLC after storage of TMETN (neat or in ethanol) for a period of nine weeks.[7]

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[3] Wheeler, CR. Nitrocellulose-Nitroguanidine Projects. Laboratory Notebook #84-05-010, p. 51. Letterman Army Institute of Research, Presidio of San Francisco, CA.

[4] Wheeler, CR. Nitrocellulose-Nitroguanidine Projects. Laboratory Notebook #84-05-010.2, p. 67. Letterman Army Institute of Research, Presidio of San Francisco, CA.

[5] *Ibid.*, p. 68.

[6] Wheeler, CR. Nitrocellulose-Nitroguanidine Projects. Laboratory Notebook #84-05-010, p. 72-75. Letterman Army Institute of Research, Presidio of San Francisco, CA.

[7] Wheeler, CR. Nitrocellulose-Nitroguanidine Projects. Laboratory Notebook #84-05-010.1, p. 34. Letterman Army Institute of Research, Presidio of San Francisco, CA.

Appendix B: ANIMAL DATA

Species: *Oryctolagus cuniculus*

Strain: New Zealand White (albino)

Source: Elkhorn Rabbitry
5265 Starr Way
Watsonville, CA 95076

Sex: Male and female

Age: Young adult

Animals in each group: 5 males and 5 females

Condition of animals at start of study: Normal

Body weight range at dosing: 2.5 - 3.0 kg

Identification procedures: Ear tattoo.

Pretest conditioning:

1. Quarantine from 11 - 29 October 1984
2. Animals were close-clipped and examined 24 hours before dosing

Justification:

The laboratory rabbit is a proven mammalian model for dermal toxicity studies because of its size, ease of restraint, and skin permeability.

Appendix C: HISTORICAL LISTING OF STUDY EVENTS

DATE	EVENT
11 Oct 84	Animals arrived at LAIR. They were tattooed and observed for illness and held for a two-week quarantine period.
11 Oct - 13 Nov 84	Animals were observed daily.
12,19 Oct 84	Animals were weighed.
24 Oct 84	Animals were removed from quarantine and transfered to the GLP Suite, examined and weighed.
29 Oct 84	Animals were close-clipped.
30 Oct 84	Animals were weighed and dosed.
31 Oct - 12 Nov 84	Animals were observed twice daily for clinical signs and the application site was scored daily.
6,13 Nov 84	Animals were weighed.
13 Nov 84	Feed was removed during the morning observation. Animals were submitted to the Necropsy Suite.

Appendix D: BODY WEIGHT DATA

Animal Number	Day Q1	Q8	Q14	0	7	14
			Females			
84F605	2185*	2555	2537	2906	2960	3146
84F606	2030	2415	2345	2661	2893	3080
84F607	2040	2505	2402	2943	3003	3075
84F608	2235	2685	2681	2468	2675	2751
84F609	1990	2400	2282	2861	2878	3004
Mean	2096.0	2512.0	2449.4	2767.8	2881.8	3011.2
Standard Deviation	107.2	116.0	160.1	199.9	126.2	153.9
			Males			
84F612	2410	2845	2876	2982	3136	3178
84F613	2185	2610	2640	2786	2738	3001
84F614	2155	2595	2712	2847	2904	3079
84F615	2230	2620	2711	2912	2955	3155
84F617	2285	2730	2693	2787	2881	2898
Mean	2253.0	2680.0	2726.4	2862.8	2922.8	3062.2
Standard Deviation	100.5	106.6	88.6	84.4	143.8	115.1

* Weights are given in grams.

Appendix E: INDIVIDUAL DERMAL SIGNS

Animal Number	Dermal Signs	Duration of Dermal Signs(Days)	Severity*	Area†
		Females		
84F605	Erythema	1	B	5
84F606	Erythema	1	B	5
84F608	Erythema	0<,1	B	5
84F609	Erythema	1	A	5
84F610	Erythema	1	A	4
		Males		
84F612	None			
84F613	None			
84F614	None			
84F615	Erythema	2-5	A	4
84F617	Erythema	1	A	4

* Severity Scores

A = Very Slight
B = Slight
C = Moderate
D = Well-defined
E = Severe

† Pertains to percent of exposed area exhibiting signs of dermal irritation. This value is determined by visual approximation.

1 = 5%
2 = > 5 to 10%
3 = >10 to 25%
4 = >25 to 50%
5 = >50%

< Irritation attributed to razor burn.

Appendix F: PATHOLOGY REPORT

Pathology Report

13 Nov 84

ID#: GLP Study 84038

Type: Acute Dermal Toxicity (LD50) Test

Investigator: Dr. Morgan, Toxicology Group

Compound: TMETN (Case No., 3032-55-1), 9th CI Name 1,3- Propanediol, 2-Methyl - 2 [(Nitroxy) Methyl]-, dinitrate (ester).

History: Ten rabbits, 5 each male and female, (NZW) were exposed to the test compound IAW LAIR SOP-OP-STX-30. All animals were killed; tissues were taken for histological evaluation and gross necropsies were done.

Animal ID#	LAIR Path #	Sex	Gross Findings
84F605	36286	F	None
84F606	36287	F	None
84F608	36288	F	Otitis Media, Purulent, Right Ear
84F609	36289	F	Cecum - Pinworms
84F610	36290	F	Cecum - Pinworms
84F612	36291	M	Cecum - Pinworms
84F613	36292	M	None
84F6 4	36293	M	Cecum-Pinworms, Liver - Fibrous scar, capsule, lobe
84F615	36294	M	Cecum - Pinworms
84F617	36295	M	Teeth malocclusion

Histological Results of Liver Lesion:

Hepatopathy, multifocal, moderate to severe, fibrosing with giant cell formation, mineralization and vascular and lymphatic dilitation, central lobular region, liver, NZW rabbit.

Appendix F (cont): PATHOLOGY REPORT

Pathology Report
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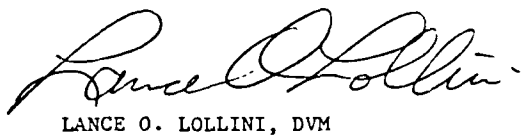
Cause: Unknown

Syndrome : None

Gross Comments: All lesions including the liver lesion were considered as incidental findings and not related to the compound being tested. The Hepatopathy seen in one rabbit could have been caused by a toxic or ischemic event which occured from two weeks to a month previous to the necropsy. The lesion was most severe in one lobe of the liver and other lobes were minimally to moderately involved. This pattern could arise form a perfusion problem such as those seen in developmental vascular defects. The cause was not apparent at necropsy.

Histology Skin: Two control and two treated sections were examined from each rabbit. All sections control and exposed were unremarkable and no compound related lesions were seen.



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